NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2005

PLAN FOR HIV-RELATED RESEARCH

VII: HIV PREVENTION RESEARCH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

HIV Prevention Research

SCIENTIFIC ISSUES

As the HIV/AIDS epidemic continues to expand in areas and populations already affected and to spread into new communities in the United States and globally, primary prevention of new HIV infections must remain a high priority. Successful HIV prevention efforts throughout the world have been grounded in scientific research on the biological, behavioral, and social determinants of HIV-related risk and protection and the consequences of HIV infection for individuals and societies. Research-based prevention strategies have contributed to the maintenance of low seroprevalence rates in a number of settings and to declining HIV epidemics in specific populations.

A major goal for the NIH is to develop further an HIV prevention research agenda that is coordinated and comprehensive and includes and combines biomedical, behavioral, and social science approaches, leading to practical, evidence-based HIV prevention strategies for public health implementation. Thus, the NIH HIV prevention science agenda focuses on three key components: behavioral and social interventions (e.g., one-on-one, couple, or group counseling for increasing condom use, street outreach efforts to reduce drug-use-related risk, and social marketing of condoms); biomedical technologies (e.g., sexually transmitted disease [STD] treatments, topical microbicides, condoms, sterile needles and syringes, and anti-addiction medications); and vaccines, integrated where appropriate. (*Note*: Because vaccine and microbicide research receive significant attention elsewhere in this Plan, the HIV prevention research agenda discussed here focuses

chiefly on other components. Please refer to the Vaccines Area of Emphasis and the Microbicides Area of Emphasis for additional details.)

HIV prevention science activities are driven by the epidemiology of HIV transmission both domestically and internationally and by the state of scientific knowledge and methods. Moreover, these activities take into account the following overlaying factors: population (defined by geography, ethnicity, gender, age, socioeconomic status, or other demographic characteristics); route of HIV transmission (sexual, parenteral, or vertical); and level of social organization targeted (individual, couple, family, network, community, or society).

PRIORITY FOR FUTURE RESEARCH:

- **Examine the ways in which social, economic, cultural, and environmental conditions, including stigma and discrimination, contribute to, or create sources of, HIV-related risk; and develop interventions based on this understanding.**

The NIH's HIV prevention research activities include both basic and intervention studies. Research that elucidates the fundamental mechanisms of human behavior, social organization, and disease transmission and progression provides essential bases for the development of testable interventions. Such studies include those that examine the range and interaction of biological, neurological, psychological, familial, social network, and other environmental factors that have an impact on HIV transmission, acquisition, or protection. While historically in the HIV/AIDS epidemic a great deal of attention has been paid to factors operating at the individual level, recently the focus has broadened to include more social and cultural factors. Not the least of these are stigma and discrimination, sociocultural beliefs and practices that often attend to physiological differences, diseases, or conditions. Any attempts to prevent HIV infection or to ameliorate its consequences for individuals or groups will have to attend to the role such negative beliefs (and their institutionalization in practice) play in exacerbating the epidemic in different settings.

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate the prevention-treatment interface, including the effects of HIV/AIDS treatment availability, delivery, success, and failure on HIV transmission and acquisition, and the integration of prevention into clinical care.**

As access to effective HIV treatments expands throughout the world and HIV-infected persons look forward to longer, healthier lives, the

lines between HIV care and HIV prevention become less distinct. A timely issue is the specific relationship between use of antiretroviral therapy (ART) and HIV transmission. A current hypothesis is that, because ART reduces viral burden (at least in blood), it may render individuals less infectious, which potentially would reduce HIV transmission and acquisition at both the individual and the population levels. However, to test this hypothesis, we will need to examine the pharmacodynamics of ART; the biology of HIV transmission and acquisition; the psychological, social, and environmental dynamics of HIV transmission and acquisition; and the epidemiological impact of widespread ART use in the context of these biological, behavioral, and social dynamics—simultaneously and longitudinally. This kind of multidisciplinary investigation increasingly is necessary in HIV prevention research.

Access to, and quality of, health care and prevention services for HIV-infected individuals are fundamental to HIV prevention. However, much remains to be learned about the dynamics of the caregiving relationship, particularly in the context of changing health care delivery systems, in which communication between patient and provider is central to managing HIV infection and preventing further transmission. This is particularly important in the context of new and improved anti-HIV therapies, which require adherence to prescribed medication regimens for optimal effect.

There is still much to be learned about the role of adherence or nonadherence to prescribed regimens on disease progression, including the interaction of ART and other medications and/or illicit drugs. Research also is underway to explicate and address further the roles of a range of potential cofactors of HIV disease progression, including other infectious and noninfectious diseases; mental health or illness; addiction to, or abuse of, alcohol and other drugs; social stigma; and the presence or absence of social support. Such research recognizes that these factors interact and contribute to the complexity of designing effective interventions for secondary HIV prevention.

PRIORITY FOR FUTURE RESEARCH:

- **Further explore, develop, and evaluate alternative methods to the randomized controlled trial (RCT) for testing the efficacy of multidisciplinary HIV preventive interventions when RCTs are inappropriate or impossible to conduct; and develop guidelines to inform the field about when such non-RCT methods are appropriate to employ.**

Over the past two decades, NIH-supported researchers and others have developed and tested numerous HIV preventive interventions with proven efficacy. Together, such interventions have reduced the incidence of unprotected intercourse, reduced the number of sex partners, delayed sexual initiation, reduced the incidence of STDs, diverted individuals from injecting drug use into drug treatment programs, reduced needle sharing and the frequency of drug injection, reduced HIV transmission from mothers to infants, and reduced (indeed, in the United States, nearly eliminated) HIV transmission through blood products.

Notwithstanding the important advances made to date, a number of methodological and ethical issues pose challenges to the further development of HIV prevention research. For example, it remains difficult, if not impossible, to observe directly and measure the kinds of human behaviors that contribute to HIV transmission and acquisition, that is, behaviors related to sex and drug use, which are private and sometimes illicit. Moreover, to demonstrate the efficacy of preventive interventions with HIV incidence outcomes in RCTs, large sample sizes in settings with significant HIV seroprevalence rates are necessary, but these are not easily obtainable. Because of these limitations in direct observation and measurement, we must rely on indirect measures, particularly, self-reported behavior and surrogate biological markers (e.g., other STDs) in many studies. Methodological research is necessary to improve continually the capacity and validity of both self-report and biological markers as measures of HIV risk behavior and disease incidence. Improvements also are needed in our capacity to detect HIV infection and to quantify HIV in genital secretions by developing better testing, screening, and measurement technologies.

HIV prevention research—whether RCT or not—must be culturally appropriate and ethically sound. Informed consent remains a bedrock of ethical research among humans. However, consensus does not exist on what constitutes "truly" informed consent, particularly when study participants may be illiterate or speak a different language from the researchers, or have cultural beliefs that do not allow for questioning scientific authority. Because HIV prevention research involves sensitive issues, the social as well as medical consequences of research participation must be well understood by study volunteers. Sensitivity to these factors is essential to ensure truly informed consent.

In the case of RCTs of preventive interventions, a particularly timely ethical and methodological issue relates to the choice of control condition. As prevention research progresses and new strategies and technologies are proven effective, accepted standards of care change. While such changes

are applauded for their preventive capabilities, they also make it increasingly difficult to measure effects of other—perhaps better—prevention strategies tested in a trial in which they are used. For example, the proven effectiveness of latex male condoms for preventing HIV transmission requires that such condoms be made available and that advice about using them be given to all participants in HIV prevention trials. However, the very use of condoms by participants in both the control and the experimental groups of a trial may mask the potential, separate effect of other prevention technologies, such as microbicides or vaccines, used by the experimental group. This dilemma poses a significant challenge to HIV prevention researchers who are attempting to develop preventive interventions with the greatest public health impact.

PRIORITY FOR FUTURE RESEARCH:

- **In collaboration with other governmental and nongovernmental organizations, enhance support for operations, health services, and evaluation research on the design, adaptation, testing, and implementation of evidence-based HIV prevention strategies; and assess the impact of such strategies on risk behaviors at the population level.**

As we enter the third decade of the HIV/AIDS epidemic, it remains essential to sustain commitment to HIV prevention by recognizing advances made so far; maintaining effective technological, behavioral, and social strategies; developing new strategies; and scaling up from limited to more widespread implementation of them. Ongoing research is necessary to ensure that a number of successful HIV prevention interventions are available to employ in combination for the greatest effect. These interventions must be available to both HIV-uninfected and HIV-infected individuals.

As HIV preventive interventions are proven effective in research settings, they must be transferred to community-based organizations (CBOs) and health service settings. At the same time, in order for these interventions to be appropriate and relevant, they must reflect the perspectives of communities that will employ them. Thus, it is imperative to develop and nurture collaborative relationships among HIV prevention researchers, practitioners, and CBOs throughout all phases of research design, development, testing, evaluation, and replication. It also is necessary to extend these relationships to health care providers, policymakers, and community constituencies in order to scale up the implementation of science-based interventions to reach a wider population. Further research is needed on how best to establish and utilize the collaborative linkages, as well as to achieve timely, effective, and efficient translation, transfer, and

scale-up. This will include needed attention to whom should be involved and responsible, and what expertise, mechanisms, and resources are necessary to foster their work.

Additional research also is needed on how best to overcome any structural or organizational barriers to greater implementation and integration of effective HIV preventive interventions. Many individuals, organizations, and social institutions still are reticent to endorse and adopt proven HIV prevention programs. Such resistance may have its roots in historical, political, religious, or cultural orientations. At the institutional level, for example, health care systems historically have been set up to provide care and treatment, and providers in those systems are trained for that purpose. To now ask such systems and providers to integrate prevention services requires rethinking and restructuring their missions, cultures, and staffing. It is not unusual for any institution to resist this kind of change. Moreover, in many communities and settings, HIV prevention efforts are resisted because of the significant stigma attached to HIV/AIDS as a disease, to the behaviors by which HIV/AIDS is contracted and transmitted, and, by extension, to the people who have it. It is important to understand and address the sources of such stigma in order to combat them and to effect greater implementation of HIV prevention strategies.

The production and implementation of high-quality HIV prevention research requires an adequate cadre of well-trained scientists and appropriate infrastructure for conducting studies. (*Note*: Please see the Training, Infrastructure, and Capacity Building Area of Emphasis in this Plan for more specific descriptions of NIH efforts in this regard.) The NIH continues to support a robust program of training opportunities for intramural and extramural research and for domestic and international work. The particular challenge for HIV prevention research is to develop new models and mechanisms of training that will promote and reward meritorious multidisciplinary work. This requires collaboration among scientists from very different disciplines, methods, and cultures, who not only must be respectful of each other's orientations, but also must become conversant in new fields. Such collaborations are necessary to ensure that high-quality HIV prevention studies are designed, succeed in peer review, and are implemented and evaluated with scientific integrity.

Key to the development of prevention researchers is the existence of adequate and appropriate infrastructure to support their work. This includes laboratory and clinical capacity, as well as data collection, management, and analysis technologies. The NIH has developed a number of these mechanisms for providing infrastructure support in both domestic

and international settings, but these mechanisms must be enhanced as technologies advance and needs change. In resource-poor settings, support for basic infrastructure, such as roads, water, and electricity, may be needed before the HIV prevention research infrastructure can be built. The NIH seeks to be helpful in assessing these needs and, where essential infrastructure and other elements exceed the mission of the NIH, to build partnerships with appropriate groups and agencies, both domestically and internationally.

In all cases, capacity building in human resources and physical infrastructure must reflect attention to ethical principles in the conduct of research and cultural appropriateness of particular projects or kinds of studies.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Elucidate the complex relationships among biological, behavioral, social, and environmental factors associated with risk of and protection from HIV transmission and acquisition, in order to prevent the spread of HIV infection.

STRATEGIES:

- Evaluate HIV transmission and acquisition in relation to the following:
  - Viral factors, such as viral concentration in blood, genital, rectal, and oral secretions, and at mucosal sites; characteristics of HIV (genotype, phenotype, and drug resistance); and HIV infection stage.
  - Protective factors at the intrinsic, extrinsic, individual, or community level (e.g., skill building and/or development of community norms) that impart resilience to exposure and infection.
  - Host intrinsic factors, such as endogenous hormonal states, mucosal immunity, and immunologic and genetic determinants.
  - Extrinsic factors, including circumcision, intercurrent sexually transmitted diseases (STDs) (both viral and bacterial), exogenous irritants, other causes of oral and anogenital inflammation, contraceptive use, nutrition, hormone replacement therapy, drug use, and pre-existing infection with other microbial agents.
  - Therapeutic factors, such as immunomodulators, antibiotics for other infectious agents, antiretroviral therapies (ARTs), and vaccines.
  - Social and ecologic factors associated with infection or protection from infections, including demographic variables (such as socioeconomic status, race, ethnicity, culture, age, community and neighborhood), physician expertise, and access to health care, and new and/or emerging factors associated with infection such as Internet access as a means to plan sexual encounters and form new sexual partnerships.
- Evaluate the effects of sexual activity, anogenital hygiene practices, and contraception choices on STD/HIV transmission.
- Understand and evaluate the occurrence of transient HIV infection and the mechanisms by which it may occur.

- Study the molecular epidemiology and effects on HIV transmission of infection with different subtypes, multiple subtypes, and recombinant viruses.
- Identify and characterize the factors related to resistance to HIV infection, including genetic, immunologic, virologic, and nutritional factors, in persons who remain uninfected despite perinatal, breastfeeding, sexual, or parenteral exposure.
- Develop appropriate nonhuman primate animal models to study the biology of transmission, so that studies are more directly relevant to HIV transmission in humans.
- Evaluate the risk of vertical, sexual, and parenteral transmission of drug-resistant strains of HIV.
- Study the relationship among viral characteristics (quantitative, qualitative, drug resistance, phenotype/genotype) of both cell-free and cell-associated HIV in genital secretions and their association with risk of sexual transmission.
- Develop reproducible, sensitive, specific, low-technology, cost-effective assays to detect and quantitate the amount of cell-free and cell-associated virus in body fluids, including breast milk.
- Develop new models of behavioral change that integrate biological, psychological, and social perspectives to explain and predict the acquisition and maintenance of HIV-related behaviors among vulnerable individuals and understudied groups across the life course and in domestic and international settings.
- Support studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure on social behaviors (e.g., mother-infant attachment and peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV; such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual and physical abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities, and study how HIV risk might change over time as a function of developmental and life-course events, such as determining one's sexual identity (e.g., "coming out"), adolescence, childbearing, marriage, divorce and separation, and aging.

- Conduct research on decision-making processes that relate to sexual and drug-related risk taking across the life course (e.g., individual and dyadic decision-making processes concerning whether and under what circumstances to have sexual intercourse; risk assessment of self and partner; the weighing of pregnancy prevention, HIV prevention, and relationship goals in choosing to use a condom and/or other method) and decision-making processes related to initiation of injecting drug use, sharing needles or other drug paraphernalia, and having sex with someone who may be infected.

- Support multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injecting drug use and the transition from noninjecting to injecting drug use (or from injecting to noninjecting drug use) as they relate to HIV transmission; such research may also include studies that investigate the relationship between any drug use and sexual risk behaviors.

- Evaluate the impact of ART use, including associated adherence dynamics, on HIV infectiousness and transmission.

- Investigate the impact on risk behavior and HIV transmission of intensive combination or new antiretroviral regimens during all phases of HIV infection.

- Investigate the characteristics and behaviors of potential "bridging" populations (e.g., bisexual men and sexually active injecting drug users) that may influence HIV infection rates among different groups.

- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including concurrent STDs, bacterial vaginosis, chorioamnionitis, nutritional deficiencies, mode of delivery, and breastfeeding.
- Investigate the mechanisms and timing of perinatal HIV transmission (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to decrease perinatal transmission.
- Evaluate the influence of drug-resistant virus in the mother on the efficacy of regimens to prevent perinatal transmission.
- Study the effect of antiretroviral regimens used for maternal health indications on the risk of vertical transmission and on other outcomes, including developmental milestones in offspring.
- Investigate interactions among drugs of abuse, anti-addiction therapy, and HIV therapeutics in pregnant women, and their impact on vertical transmission of HIV.
- Support collaborative analyses of existing databases to evaluate potential obstetric interventions, such as cesarean deliveries and other aspects of intrapartum care, to prevent vertical transmission.
- Further evaluate the risk and benefit of cesarean delivery for reducing HIV transmission (e.g., evaluate the risk of postpartum morbidity in infected women with elective cesarean delivery and determine whether additional benefit of cesarean delivery for preventing transmission accrues in women receiving ART).

OBJECTIVE - B:

Develop and test innovative HIV preventive interventions—individually and in combination—for both HIV-infected and HIV-uninfected populations.

STRATEGIES:

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions in different domestic and international settings and populations to reduce high-risk HIV-related sex and drug-use behaviors and HIV transmission.
- Continue development of interventions targeting at-risk populations (e.g., injecting drug users [IDUs], other drug users, partners of drug users, and men who have sex with men), with particular emphasis on drug use and sex-related risks.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission.
- Develop and assess the effectiveness of utilizing multiple approaches, both individually and in combination, that may decrease HIV transmission among at-risk groups such as adolescents, men who have sex with men, and substance users.
- Develop and test interventions targeted at HIV-infected persons to reduce their risky sexual and drug-use behaviors.
- Support research to increase the effectiveness, cost-effectiveness, and cost-utility of interventions for HIV-related drug abuse, mental health, alcoholism treatment, and family planning, and to improve access to these treatments and interventions; such research may include the development of new pharmacotherapies and behavioral therapies to reduce HIV-related risk behavior and HIV transmission in different settings and populations.
- Support domestic and international intervention research to enhance healthy sexual development and responsible protective behaviors (including access to and use of barrier methods, avoidance of too-early or nonconsensual sex, and abstinence from unsafe sexual behavior) throughout one's lifetime.

- Support interventions for populations that are currently low risk or that perceive themselves to be low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors (e.g., non-sexually active, non-drug-using adolescents; heterosexual men and women; middle-aged and older populations; and racial/ethnic communities with low HIV prevalence rates).

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization (individual, dyad, family, network, community, institution, and society) and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts and settings (e.g., urban versus rural populations).

- Examine the impact of population-level interventions (e.g., social normative behavior changes, economic opportunities for women, mass or syndromic approaches to STD control, early treatment of HIV infection, and use of family planning programs to diagnose and treat STDs) on HIV transmission in international and domestic communities.

- Develop, test, and evaluate interventions that target individuals both within prisons and returning to society from the prison system. Such strategies include increasing access to education, information, therapeutic care, prevention services, and clinical trials.

- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.

- Develop intervention strategies focused on prevention of comorbid or linked conditions in at-risk populations (e.g., HIV and hepatitis C in IDUs).

- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention intervention research.

- Support the discovery, development, preclinical, and clinical evaluation of new, improved, acceptable, effective, and safe chemical and physical barrier methods, including topical microbicides and other methods, to reduce sexual transmission of HIV and STDs.

- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STDs.
- Develop and assess safe and effective formulations and modes of delivery, including applicators, for microbicides.
- Develop and support *ex vivo* and animal models to evaluate the safety and efficacy of chemical and physical barriers, including topical microbicides, for prevention of mucosal HIV transmission.
- Develop and evaluate strategies to prevent transmission of HIV through breastfeeding/breast milk.
- Develop safe and conveniently administered strategies to interrupt maternal-fetal transmission of HIV using interventions that are widely affordable in developing and resource-poor nations.
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring without compromising treatment of the pregnant women; such strategies may include, alone or in combination, antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, antiretrovirals, and microbicides.
- Support the long-term followup of women and children (including children ultimately found to be uninfected) who participate in perinatal HIV prevention trials to evaluate possible late effects of antepartum ART.
- Develop strategies to prevent blood-borne transmission of HIV in health care settings, including blood screening strategies and technologies, and the role (i.e., use/misuse) of transfusion and injections.
- Evaluate new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion and other parenteral exposures in health care settings (e.g., vitamin and medication injections) in developing and developed countries.
- Evaluate the potential risks and benefits of providing prophylaxis against infection after occupational and nonoccupational exposures to HIV.

- Develop and evaluate biomedical and behavioral interventions for screening, diagnosis, and treatment of STDs as a means of preventing HIV transmission.
- Support research to identify and address potential adverse outcomes of efficacious prevention interventions after the interventions are widely disseminated.

OBJECTIVE - C:

Identify and address issues associated with the initiation, sustainability, and adaptability of HIV prevention efforts among individuals and communities over time.

STRATEGIES:

- Evaluate the effects of access to, acceptability of, and adherence to prevention interventions on perinatal, sexual, and drug-use-associated transmission of HIV.
- Support behavioral and social research on the acceptability, access, and utilization of biomedical HIV prevention methods (e.g., male and female condoms, microbicides, and vaccines).
- Support intervention research that attends to contextual risk factors for individuals and groups that are disproportionately affected by HIV infection and that demonstrate high-risk behaviors.
- Support basic and pre-intervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.
- Develop and assess interventions designed to motivate and sustain safer sex and negotiated safety among HIV-infected persons in the context of ART at the individual and community levels.
- Support policy-oriented research, including research into how to reach and influence policymakers and other decision makers to examine and adopt appropriate, evidence-based HIV prevention, treatment, and care measures.

OBJECTIVE - D:

Support research to better understand and mitigate the physical, psychological, and social consequences of HIV infection and disease progression on individuals, dyads, and groups (e.g., families, networks, and communities).

STRATEGIES:

- Evaluate the potential long-term complications of vaccines, microbicides, ART, and other therapies used to reduce HIV transmission on the development of chromosomal damage, mutagenesis, carcinogenesis, or teratogenesis.
- Study and develop effective prevention and treatment strategies for persons who subsequently become HIV-infected despite the administration of HIV vaccines.
- Advance cell- and gene-based therapies in neonates and young children that may restore immune function and control viral load.
- Conduct basic behavioral research to understand better the impact of HIV therapeutic regimens on adherence, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., people feeling better and healthier) among HIV-infected individuals.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.
- Support research on the economic and social implications for youth and older persons who provide support and care to family members or friends with HIV/AIDS and their dependents.
- Investigate the role in pathogenesis of potential cofactors, correlates, and mediators of disease progression, including gender, immunological factors, infectious agents, hormonal factors, nutritional factors, drug use, re-exposure to HIV, and interventions such as nutritional supplementation, exercise, and other health-enhancing behaviors.
- Investigate how different patterns of adherence to drug regimens in treatment-experienced and treatment-unexperienced populations contribute to HIV drug resistance and affect disease progression and transmission of resistant virus.

- Study the effectiveness of adherence interventions in a range of populations (e.g., racial/ethnic minority, adolescent, women, men who have sex with men, transgender, drug-using, and mentally ill populations).
- Study once-daily ART regimens in resource-poor settings with respect to adherence, toxicity, clinical outcomes, need for and impact of laboratory monitoring, and risk behaviors.
- Study the effects of nutritional deficiencies, oxidative stress, and body composition on HIV disease progression.
- Develop low-cost/low-burden viral load and CD4 tests for monitoring patients receiving antiretroviral medications in resource-constrained settings.
- Investigate the influence of HIV viral factors, including genotype, phenotype, and HIV drug resistance, on disease progression.
- Study HIV-infected infants, children, and adolescents to determine: (1) factors related to divergent rates of disease progression, (2) mechanisms that contribute to impaired growth and neurodevelopment, (3) the physical and emotional impact of childhood infectious diseases and the safety and efficacy of immunizations for these diseases, (4) childhood- and adolescent-specific complications, and (5) the impact of medical and behavioral treatment interventions on the items listed above.
- Evaluate the rate of HIV disease progression in conjunction with the effects of feasible interventions for delaying or preventing progression in international settings or populations with different viral clades and possible cofactors such as nutrition and opportunistic infections (OIs).
- Assess the effectiveness and impact of immunizations and co-infections with hepatitis C, tuberculosis (TB), and other infectious agents on disease progression in HIV-infected populations.
- In HIV-infected populations, evaluate risk factors and develop and assess interventions that reduce or prevent the following: other infectious diseases, malignancies and associated oncogenic infections, negative consequences of treatment interventions, and other HIV-associated diseases, including central and peripheral nervous system diseases, cardiovascular manifestations, oral and mucosal lesions, and wasting and other metabolic disorders.

- Test and evaluate interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.
- Examine the impact of access to health care and of adherence to therapeutic regimens on health outcomes in HIV-infected populations.
- Evaluate the possible interaction of ART, treatment for drug use/abuse, and other infections (e.g., hepatitis C virus) on HIV disease progression and resulting treatment recommendations.
- Support research on adherence to treatment regimens, including communication techniques to improve shared decision making between health care providers and HIV-infected individuals, issues such as how and when to initiate therapy, and behavioral strategies to manage symptoms secondary to treatment protocols.
- Explore low-cost, low-technology interventions, including nutritional interventions and better prophylaxis and treatment of OIs, for preventing HIV disease progression among persons in developing countries.
- Study the emergence and re-emergence of infectious diseases and the development of antimicrobial-resistant infections, such as multidrug-resistant TB, in HIV-infected populations.
- Evaluate the impact of interactions between and among drugs of abuse, anti-addiction therapy, and HIV therapeutics on maternal disease progression during pregnancy and postpartum.
- Support research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection. These barriers may impede access, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).

- Develop and test interventions to modify the practice behaviors of health care providers to improve the quality of screening, counseling, and treatment services for HIV-positive persons and persons at risk for HIV infection.
- Support research on the decision-making processes of health care workers in screening and identifying HIV cases, especially cases of early and acute infection.
- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations in coping with HIV infections, maintaining quality of life, and avoiding engagement in HIV-related risk behaviors.
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including their decisions regarding treatment and quality of life.
- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout.

OBJECTIVE - E:

Support research that addresses methodological and ethical issues in the conduct of HIV prevention studies, including studies that are cross-cultural, multidisciplinary, and multimodal.

STRATEGIES:

- Develop and validate sensitive, specific, and reproducible methods for quantifying HIV in genital secretions.
- Design and test behavioral interventions to increase recruitment, retention, and adherence to biomedical and behavioral HIV prevention research protocols among both HIV-infected and uninfected individuals.
- Develop and evaluate methods to access, recruit, and retain at-risk populations (e.g., racial/ethnic minorities, adolescents, women, men who have sex with men, transgenders, commercial sex workers, substance users, and the mentally ill) for preventive intervention studies.
- Support, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV preventive intervention research.
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use in HIV prevention research: self-report measures, HIV infection, and other disease outcomes such as other STDs and blood-borne diseases.
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.
- Develop, strengthen, and evaluate culturally, linguistically, and age sensitive and appropriate research instruments for subpopulations (e.g., HIV-infected children, the elderly, and prisoners).
- Develop improved methodologies—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.

- Support research to determine how self-reported outcome measures are affected by "response shift," including the effects of disease progression and treatment on the criteria individuals use to appraise their quality of life, and the impact of interventions on participants' standards for judging their degree of risk, level of skills, and adequacy of support and care.
- Develop and refine techniques for measuring social networks associated with HIV transmission and prevention.
- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and the factors that influence behaviors and behavior change.
- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.
- Develop improved sampling strategies for subpopulations (e.g., children and adolescents, drug users, the elderly, and gay men of color) in HIV prevention studies.
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and HIV-infected populations, including improved followup methodologies, methods to increase followup rates, and methods for dealing with subject attrition, missing data, and non-normal distributions.
- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of intervention strategies at the individual, group, and community levels.
- Encourage secondary data analysis and meta-analysis, and develop approaches to protect and document confidentiality in HIV prevention studies.
- Develop and refine research techniques to advance multisite, intercultural, and international HIV prevention studies.
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention interventions.

- Support training in ethical issues related to the conduct of research in both developed and developing countries.
- Develop models of research collaboration and capacity building among researchers and community-based organizations.
- Evaluate the effects of legal and ethical constraints on methods of HIV prevention research and service delivery, particularly among adolescents, children, men who have sex with men, transgenders, commercial sex workers, psychiatric populations, prisoners, immigrants, and other vulnerable or special populations.
- Identify and validate methods to ensure informed consent, including approaches that provide for sustained knowledge of the nature of the study among participants.
- Clarify and develop methods to achieve community consent, where appropriate, particularly for cluster randomization trials.

OBJECTIVE - F:

Support research to understand better how to implement evidence-based HIV preventive interventions. Identify and evaluate strategies for translating proven/effective interventions into public health practice, including the integration of prevention into clinical care.

STRATEGIES:

- Support research in the United States and abroad to improve the transfer of effective HIV interventions to and from communities and their associated health care systems. In particular, support research on the adoption and adaptation of efficacious HIV interventions by communities (e.g., studies of diffusion processes and the exchange of knowledge between service providers and researchers). This research should examine the maintenance of effective interventions and generalizability of interventions with diverse populations.
- Support research that investigates the impact of laws, guidelines, and policies on HIV transmission and prevention.
- Support research to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, family planning, and social services that reduce HIV risk behaviors and HIV transmission.
- Support research to understand and improve linkage, coordination, and integration among primary medical care; drug, alcohol, and mental health treatment; STD treatment; reproductive health and family planning services; social services; and community-based HIV prevention services.
- Support research on integrating HIV prevention interventions into drug addiction treatment settings, with emphasis on behavioral treatments, alone or in combination with pharmacotherapies, for both HIV-positive and HIV-negative drug users.
- Support intervention research on strategies for changing the willingness of communities and institutions to support and adopt primary prevention interventions.
- Support research on the decision-making processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments.

- Support research to understand how and whether communities engage in HIV preventive interventions, and to determine how to better ensure the use of prevention research by communities, health care and public health organizations, and policy planners in the United States and abroad.
- Develop and refine research techniques for measuring and evaluating responses by organizations to HIV and for characterizing organizations working in the HIV field.
- Improve methods for forecasting and modeling AIDS caseloads, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs.
- Develop and evaluate mechanisms for disseminating behavioral research findings to the HIV/AIDS research and service communities, and for implementing findings in those communities.
- Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV prevention interventions in specific communities.
- Using existing and innovative methods, rapidly disseminate new research findings and information about the findings' potential implications for HIV prevention, care, and treatment among HIV-infected individuals.

OBJECTIVE - G:

Enhance capacity, training, and infrastructure for the conduct of HIV prevention research, especially in resource-poor settings.

STRATEGIES:

- Develop the capacity to identify at-risk domestic and international populations (e.g., adolescents, young adults, minorities, women, men who have sex with men, transgenders, and substance users) that have incidences and prevalences suitable for recruitment into HIV preventive intervention trials.
- Support the capacity to develop rapid-response HIV preventive intervention studies.
- Develop and maintain in HIV epicenters the infrastructure for conducting behavioral and other intervention trials.
- Provide for the long-term support of advanced in-country research and research infrastructure in developing countries participating in priority AIDS-related intervention research, such as studies of methods to prevent/interrupt mother-to-child, sexual, or parenteral transmission.
- Support training opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise (e.g., methods to conduct cost-effectiveness analyses, measurement of biologic outcomes in behavioral intervention studies, ethnographic and other qualitative methods, and network analysis).
- Increase training to strengthen global capacity to conduct multidisciplinary AIDS-related prevention research in developing countries.
- Collaborate with the Office of Public Health and Science and other U.S. Government agencies in the development of training in HIV prevention, treatment, research, and education for health care providers, AIDS service providers, and health educators.
- Enhance the critical mass of trained in-country HIV prevention researchers, especially in resource-poor settings.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	John E. Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities

APPENDIX B:

FY 2005 OAR Planning Group for HIV Prevention Research

FY 2005 HIV PREVENTION RESEARCH PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ACSR	AIDS and Cancer Specimen Resource, NCI
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ART	antiretroviral therapy
ARV	antiretroviral
ATI	analytic treatment interruption
ATIS	AIDS Treatment Information Service
AVEG	AIDS Vaccine Evaluation Group
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Programs for Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DHHS	Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GBV-C	GB virus (hepatitis G)
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria

GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
GRIP	Global Health Research Initiative Program, FIC
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAb	monoclonal antibody
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization

NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NK	natural killer (cell)
NMAC	National Minority AIDS Council
NNTC	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PACTG	Pediatric AIDS Clinical Trials Group
PCP	*Pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCT	randomized clinical trial, randomized controlled trial
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WRAIR	Walter Reed Army Institute of Research

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